Memorandum Supporting Proposed Decision to Approve Registration of the New Active Ingredient, Ipflufenoquin

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I. SUMMARY

This memorandum presents the rationale to support the proposed decision of the U.S. Environmental Protection Agency ("EPA" or "the Agency") to unconditionally register under 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the new active ingredient, ipflufenoquin.

Ipflufenoquin (2-{2-[(7,8-difluoro-2-methylquinolin-3-yl)oxy]-6-fluorophenyl}propan-2-ol) is a quinoline fungicide developed by Nippon Soda Co., Ltd. The company claims that ipflufenoquin's mode of action (MOA) is novel and not yet defined. Ipflufenoquin is proposed for broad spectrum disease control use against a variety of fungal diseases including *Botrytis*, *Sclerotinia*, *Colletotrichum*, scab, blast, and powdery mildew on pome fruit (Crop Group 11-10) and almonds.

Nippon Soda Co., Ltd., proposed one technical product and one end-use product be registered. Ipflufenoquin is formulated as a suspension concentrate (SC) in one single-active-ingredient end-use formulation (KINOPROL 20SC).

Application methods include aerial, airblast, ground, chemigation, and hand-held equipment. Application rates for almonds are a maximum of 0.065 lb/a.i./A (pounds of active ingredient per acre) per application and 0.195 lb a.i./A per year. For pome fruit, maximum application rates are 0.04 lb a.i./A per application and 0.12 lb a.i./A per year. The minimum retreatment interval is 7 days.

II. REQUESTED ACTION

On September 26, 2019, the EPA received an application from Nippon Soda Co., Ltd., for registration of a new fungicide, ipflufenoquin (CAS# 1314008-27-9), for use on pome fruit (Crop Group 11-10) and almonds. Nippon Soda Co., Ltd., requested reduced risk status and provided the information necessary for EPA to determine it met this requirement. Pursuant to FIFRA section 3(c)(10), EPA granted reduced risk status for the application.

Under FIFRA section 3(c)(4), EPA is required to notify the public when a request for registering a new active ingredient is made and allow a 30-day comment period. The EPA published a notice of receipt in the Federal Register for an application requesting the registration of ipflufenoquin on May 27, 2020. In addition, on May 29, 2020, the EPA published a notice of filing in the Federal Register announcing the receipt of the initial filing of the ipflufenoquin petition by Nippon Soda Co., Ltd., under the Federal Food, Drug, and Cosmetic Act (FFDCA) requesting the establishment of tolerance regulations for residues of ipflufenoquin on various commodities. One comment from the Center for Biological Diversity and two anonymous comments were received in response to the notice of receipt and no comments were received on the notice of filing. These comments will be addressed in the Agency's Final Decision document in order to respond to all comments on this action comprehensively, including comments received during the 15-day public comment period on this proposed decision.

III. USE PROFILE

Table 1 below outlines the use patterns requested for ipflufenoquin by crop. For resistance management, all uses are restricted to no more than two sequential applications.

Table 1. Requested Use Patterns for Ipflufenoquin

Use Site	Application Methods	Max Single Rate (lbs a.i./A)	Max # App/yr	Max Annual Rate lbs (a.i./A/yr)	Minimum Retreatment Interval (days)	Pre-Harvest Interval (days)
Almond	Aerial, ground, chemigation	0.065	3	0.195	7	14
Pome Fruit	Aerial, ground, chemigation	0.040	3	0.120	7	7

IV. EVALUATION

In evaluating a pesticide registration application, the EPA assesses a wide variety of exposure information (i.e., where and how the pesticide is used) and environmental-fate (i.e., how the chemical will move in the environment) and toxicity studies (i.e., effects on humans and other non-target organisms) to determine the likelihood of adverse effects (i.e., risk) from exposures associated with the proposed use of the product. Risk assessments are developed to evaluate the environmental fate of the compound as well as how it might affect a wide range of non-target organisms including humans, terrestrial and aquatic wildlife (plants and animals). In addition, a biological and economic benefits assessment may be conducted. On the basis of these assessments, the EPA evaluates the risks and benefits and determines whether additional labeling restrictions or registration conditions are needed to ensure that, when balanced against the benefits, potential risks are mitigated to meet the standard of no unreasonable adverse effects to human health or the environment.

A. Assessment of Risks to Human Health

This section summarizes the Agency's Human Health Risk Assessment. The full Human Health Risk Assessment can be found in EPA's public docket (EPA-HQ-OPP-2020-0225) at www.regulations.gov.

The EPA requires a wide range of studies in order to assess a pesticide use scenario. For the proposed uses of ipflufenoquin on pome fruit and almond, the database of studies required to support the assessment of risk to human health is complete.

1. Toxicology Profile

The hazard database for ipflufenoquin indicates that teeth, the liver, thyroid, hematological system, and intestines are the primary targets in rodents. Liver effects ranged from changes in liver weight to histopathological changes (increased single cell necrosis, bile duct hyperplasia, and hepatocellular mitotic figures). Effects in the hematological system included changes such as decreases in red blood cells, hemoglobin and hematocrits, as well as increases in spleen weight, prothrombin time and erythropoiesis of the spleen. However, these hematological effects were considered mild and occurred at the same or higher doses than the tooth effects. Intestinal findings included black content, minimal cellular infiltration in the lamina propria of the colon, minimal hyperplasia epithelium and minimal regeneration of the surface epithelium in the colon while thyroid effects were limited to follicular cell hypertrophy. Intestinal and thyroid effects occurred at the same doses where tooth effects were observed only in the subchronic studies in rats. Tooth effects including discoloration, enamel hypoplasia, dysplasia and abrasion of the incisors were observed throughout the ipflufenoquin database in rodents only. Human relevance could not be ruled out because these tooth effects observed with ipflufenoquin have been previously observed in humans as a result of exposure to ipflufenoquin. Children are considered the most susceptible population to the tooth effects since dental enamel development and formation occurs during childhood. The toxicology database showed no adverse toxicological effects were observed in dogs.

Acute toxicity studies show that ipflufenoquin exhibits low acute toxicity via the oral (Toxicity Category III), dermal (Toxicity Category III) and inhalation (Toxicity Category IV) routes of exposure. Ipflufenoquin is slightly irritating to the eye (Toxicity Category IV), non-irritating to skin (Toxicity Category IV), and it is not a dermal sensitizer.

No acute dietary endpoint was selected because the effects observed in the acute neurotoxicity (ACN) study occurred at doses not relevant for risk assessment and no other acute effects were observed in the database. The chronic dietary endpoint was selected from the chronic/carcinogenicity study in mice with a no-observed-adverse-effect level (NOAEL) of 30 mg/kg/day (lowest-observed-adverse-effect level [LOAEL] = 106 mg/kg/day, based on pale teeth and broken teeth).

The Food Quality Protection Act Safety Factor (FQPA SF) was reduced to 1x based on the following considerations: (1) the toxicity database is considered complete to characterize potential pre- and postnatal risk for infants and children; (2) no reproductive effects were observed in rats; (3) although there were offspring effects in the reproductive study, they occurred only in the presence of parental toxicity; (4) there were no developmental effects in the developmental studies in rats and rabbits; (5) although potential signs of neurotoxicity were observed in the ACN study, clear NOAELs/LOAELs are established and effects occurred at high doses that are not relevant for risk assessment purposes; and (6) the points of departure selected for risk assessment purposes are protective of the offspring and potential neurotoxic effects seen in the database. Furthermore, the dietary assessments are based on conservative inputs, including tolerance level residues and modeled drinking water residues, such that exposure to infants and children have not been underestimated.

See Tables 2 and 3 for additional details on end point selections.

Table 2. Summary of Toxicological Doses and Endpoints for Ipflufenoquin for Use in Dietary and Non-Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**POD**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (All Populations)	No endpoint attributable to a single dose was identified in the ipflufenoquin database.			
Chronic Dietary (All Populations)	NOAEL = 30 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Chronic RfD = 0.3 mg/kg/day cPAD = 0.3 mg/kg/day	Carcinogenicity study in mice MRID 50921038 LOAEL = 1000 ppm (equivalent to 106 mg/kg/day) based on pale teeth and broken teeth.
Adult Oral Short-Term (1-30 days)	NOAEL = 171 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	LOC for MOE = 100	13-Week oral study in rats MRID 509201025 LOAEL = 8000 ppm (577 mg/kg/day) based on hematological changes, bilateral submaxilla abrasion of the incisors, white coloration of the incisors and enamel hypoplasia of the tooth, intestinal microscopic findings and thyroid follicular cell hypertrophy in males and females.
Incidental Oral Short-Term (1-30 days)	NOAEL = 55 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	LOC for MOE = 100	13-week oral study in mice MRID 509201027 LOAEL = 1000 ppm (164 mg/kg/day) based on pale teeth and loss of enamel
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	No dermal endpoints were selected because no systemic effects were observed in the dermal study up to the limit dose. Children are not expected to be exposed based on the current exposure pattern.			
Inhalation Short-Term (1-30 days) and Intermediate-term (1-6 months)	NOAEL = 55 mg/kg/day Inhalation absorption assumed equal to oral absorption	UF_A = 10X UF_H = 10X	LOC for MOE = 100	13-Week oral study in mice MRID 509201027 LOAEL = 1000 ppm (164 mg/kg/day) based on pale teeth and loss of enamel in male and female mice.
Cancer (oral, dermal, inhalation)	Classification: "Not Likely to Be Carcinogenic to Humans" based on convincing evidence that carcinogenic effects are not likely below a defined dose range.			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population

(intraspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

Table 3. Summary of Toxicological Doses and Endpoints for Ipflufenoquin for Use in Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	No dermal endpoints were selected because no systemic effects were observed in the dermal study up to the limit dose.			
Inhalation Short-Term (1-30 days) and Intermediate-term (1-6 months)	NOAEL = 55 mg/kg/day Inhalation absorption assumed equal to oral absorption	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	13-Week oral study in mice MRID 509201027 LOAEL = 1000 ppm (164 mg/kg/day) based on pale teeth and loss of enamel in male and female mice.
Cancer (oral, dermal, inhalation)	Classification: "Not Likely to Be Carcinogenic to Humans" based on convincing evidence that carcinogenic effects are not likely below a defined dose range.			

2. Dietary (Food + Water) Risks

An unrefined chronic dietary exposure and risk assessment was conducted using tolerance-level residues, modeled drinking water estimates provided by the Environmental Fate and Effects Division (EFED), 100% crop treated assumptions, and 2018 default processing factors and empirical processing factors where available. The chronic dietary risk assessment showed no risk estimates of concern for the U.S. population or any population subgroup. The chronic dietary (food and drinking water) exposure and risk estimates for ipflufenoquin were <1% of the chronic population adjusted dose (cPAD) for the general U.S. population and all population subgroups. An acute dietary exposure assessment was not required because no endpoint attributable to a single dose was identified in the ipflufenoquin database. Ipflufenoquin is classified as "Not Likely to Be Carcinogenic to Humans" therefore, a cancer dietary exposure assessment was not required.

3. Occupational Handlers Risks

A quantitative dermal risk assessment was not conducted since a dermal point of departure (POD) was not selected for ipflufenoquin. No dermal endpoints were selected because no systemic effects were observed in the dermal study up to the limit dose. Therefore, only occupational inhalation risks were quantitatively assessed. The occupational handler inhalation level of concern (LOC) is 100. Margins of Exposure (MOEs) are calculated in such a way that a higher number indicates a lower risk to human health, and a lower number indicates a higher risk to human health. The short- and intermediate-term inhalation risk estimates for the occupational handlers resulted in no risk estimates of concern at baseline attire (i.e., no respirator) and engineering controls for aerial applications. All calculated MOEs are above 100 (MOEs= 150,000 to 40,000,000) and therefore are not of concern for handlers. The single maximum

application rate for the proposed use on almonds (0.065 lb a.i./A) is higher than the proposed single maximum rate on pome fruit (0.04 lb a.i./A), and both almonds and pome fruit have similar use patterns (i.e., orchard/vineyard); therefore, the occupational handler assessment of the proposed use on almonds is protective of all exposure scenarios for the proposed use on pome fruit.

A quantitative occupational post-application inhalation exposure assessment was not conducted. However, an inhalation exposure assessment for occupational/commercial handlers was performed as stated above. Handler exposure due to outdoor pesticide application is likely to result in higher exposure than post-application exposure. Although inhalation exposure during dusty mechanical activities such as mechanical harvesting and shaking may be another possible source of post-application inhalation exposure, the airblast applicator scenario is believed to represent a reasonable worst-case surrogate estimate. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios. Because the non-cancer inhalation risk estimate for commercial airblast application is not of concern (MOE $\geq$ 100), no concerns for post-application exposure have been identified.

Ipflufenoquin is classified as Toxicity Category III for acute oral, Toxicity Category III for acute dermal and Toxicity Category IV for acute inhalation. Ipflufenoquin is slightly irritating to the eye (Toxicity Category IV), non-irritating to skin (Toxicity Category IV), and it is not a dermal sensitizer. Under 40 CFR § 156.208(c)(2), active ingredients classified as category III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour restricted entry interval (REI). REIs may be further reduced if certain criteria are met in accordance with the Pesticide Registration (PR) Notice 95-3 [Reduction of Worker Protection Standard Interim REIs for Certain Low Risk Pesticides]. Upon review of the criteria for the active ingredient only, ipflufenoquin is consistent with the criteria in PRN 95-3 that allow for a 4-hour REI. Accordingly, the proposed label REI of 4 hours is adequate to protect agricultural workers from post-application exposures to ipflufenoquin.

4. Residential Handler Risks

A residential assessment was not conducted since there are no proposed residential uses for ipflufenoquin.

5. Aggregate Risk

Ipflufenoquin is not proposed for any residential uses at this time; therefore, the chronic aggregate exposure and risk assessment combines exposures in food and drinking water only. There are no chronic aggregate risk estimates of concern.

6. Cumulative Risk

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to ipflufenoquin and any other substances and ipflufenoquin does not appear to produce a toxic

metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that ipflufenoquin has a common mechanism of toxicity with other substances.

B. Assessment of Environmental and Ecological Risks

This section, *Assessment of Environmental and Ecological Risks*, is a summary of the standard assessment that the Agency conducts. The full Environmental and Ecological Risk Assessment can be found in EPA's public docket (EPA-HQ-OPP-2020-0225) at www.regulations.gov.

Ecological risk characterization integrates the results of the exposure and ecotoxicity data to evaluate the likelihood of adverse ecological effects. The means of integrating the results of exposure and ecotoxicity data is called the risk quotient method. For this method, risk quotients (RQs) are calculated by dividing exposure estimates by ecotoxicity values, both acute and chronic (RQ = Exposures/Toxicity). RQs are then compared to the EPA's levels of concern (LOCs). The LOCs are criteria used by the EPA to indicate potential risk to non-target organisms. The criteria indicate whether a pesticide, when used as directed, has the potential to cause adverse effects to non-target organisms.

In this proposed decision, EPA is using an interim approach to evaluate potential effects to federally endangered or threatened species ("listed species") and their designated critical habitat while the Agency continues to work towards a long-term approach for assessing new active ingredients' effects on listed species. In this interim approach, EPA is using the RQ and LOC method for listed species. See *Environmental Protection Agency, Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs* (2004) [1]. With this approach, EPA evaluates potential impacts of a proposed new active ingredient on listed species that may indicate whether a taxon is impacted by a proposed use. However, EPA is not necessarily intending to reach a completed effect determination for each listed species or critical habitat because further refinement or analysis (e.g., consideration of species-specific biological and habitat requirements, overlap with use sites) may be necessary to complete an effects determination, which may not be conducted in the risk assessment.

The database required to evaluate the environmental fate and ecological effects of ipflufenoquin is considered complete to support the assessment of ecological risk and for registration of the use patterns discussed in this document.

1. Environmental Fate Profile

It is expected that ipflufenoquin will not substantially volatilize from soil or water (maximum of 1% volatility in laboratory studies), and therefore volatilization will not be a major route of dissipation for ipflufenoquin off the field. Studies suggest that ipflufenoquin degrades rapidly through aqueous photolysis but is stable to hydrolysis. Ipflufenoquin degrades slowly in aerobic

[1] United States Environmental Protection Agency. 2004. Overview of the Ecological Risk Assessment Process in the Office of Pesticide Program, U.S. Environmental Protection Agency. Endangered and Threatened Species Effect Determinations.

and anaerobic aquatic environments, producing no major and only limited minor transformation products.

Ipflufenoquin exhibits persistence in soil and aquatic environments. The fate properties of ipflufenoquin suggest that it has the potential to bioaccumulate in aquatic food chains, however studies show low potential for bioaccumulation in fish. Available environmental fate data classify ipflufenoquin as slightly to moderately mobile. It may be transported to groundwater via leaching or to surface water via spray drift and runoff.

2. Environmental Effects

The exposure and toxicity effects data are integrated to evaluate the risks of adverse ecological effects on non-target species. EPA uses a deterministic approach or the risk quotient method to compare toxicity to environmental exposure. In the deterministic approach, a risk quotient (RQ) is calculated by dividing a point estimate of exposure by a point estimate of effects. This ratio is a simple, screening-level estimate that identifies high- or low-risk situations. Calculation of RQs are based upon ecological effects data, pesticide use data, fate and transport data, and estimates of exposure to the pesticide. In this method, the estimated environmental concentration (EEC) is compared to an effect level, such as an LC_{50} (the concentration of a pesticide where 50% of the organisms die), the no observed adverse effect level (NOAEL), and the no observed adverse effect concentration (NOAEC)[2]. The resulting ratio of the point estimate of exposure and the point estimate of toxicity, i.e., the RQ, is then compared to a specified LOC, which represents a threshold for concern. If the RQ exceeds the LOC, risks concerns are triggered. If RQs are below the LOC for non-listed species, EPA makes a finding of no risk of concern. If the RQs are below the LOC for listed species, EPA concludes that direct effects are not expected for that listed taxon. However, further refinement or analysis may be necessary to complete an Effects Determination for species within that taxon as there may be indirect effects to a listed species from potential direct effects to another taxon.

Based on the ipflufenoquin assessment, no LOC was exceeded for any non-target, non-listed organism for any of the proposed use patterns. For listed species, EPA determined that No Effects (NE) Determinations could be made for all listed species (fish, aquatic invertebrates, aquatic plants, birds, amphibians, reptiles, mammals, and terrestrial invertebrates) except for listed terrestrial plants, or those listed species that have an obligate relationship with a terrestrial plant species. At this time, EPA has not made effects determinations for listed terrestrial plants or those listed species that have an obligate relationship with a terrestrial plant species. EPA has also made NE Determinations for the designated critical habitats of all listed species, except for those listed species with defined Principle Constituent Elements (PCEs) or Physical or Biological Features (PBFs) that indicate obligate relationships to a specific terrestrial plant species, because the proposed uses of ipflufenoquin will have no discernable effect on those critical habitats. EPA has not made any effects determinations for listed terrestrial plants or those listed species or

[2] The NOEL (no observed effect level) or the NOEC (no observed effect level) has been defined in USEPA (2004) as the highest concentration of a chemical in a toxicity test that has no significant adverse effect on the exposed population of test animals. In this document, EPA refers to these endpoints more precisely as the NOAEL/NOAEC (No Observed Adverse Effect Level or Concentration) to more appropriately include the adverse effect term of the original definition of NOEL/NOEC.

designated critical habitat that have an obligate relationship with a terrestrial plant species at this time. EPA is considering additional lines of evidence to assess risks to listed terrestrial plants, including inherent variability of plant toxicity responses compared to observed effects in ipflufenoquin studies, other quinoline fungicide toxicity data, and higher tested rates compared to the proposed label rates that could be used to make determinations for listed terrestrial plants. EPA will discuss these additional analyses and any impact they have on EPA's ability to make effect determinations for listed terrestrial plants and those listed species with obligate relationships to plants in the final decision for ipflufenoquin.

For aquatic organisms, the risk assessment concluded:

- LOC exceedances did not occur for acute or chronic exposure for any listed or non-listed aquatic species, including all aquatic animals (vertebrates and invertebrates) and aquatic plants. LOC for non-listed aquatic animals is 0.5 for acute and 1 for chronic exposures. LOC for non-listed aquatic plants is 1. LOCs for listed aquatic animals is 0.05 for acute and 1 for chronic exposures and is 1 for listed aquatic plant species.
- Despite being classified on a hazard basis as moderately toxic to fish on an acute-basis, acute RQs are <0.01 for all aquatic vertebrates (fish and aquatic-phase amphibians). While effects on growth were observed in chronic fish studies, chronic RQs range from 0.01 for estuarine/marine vertebrates to 0.03 for freshwater vertebrates and are below the chronic LOC.
- Despite being classified on a hazard basis as moderately toxic to invertebrates, acute RQs for all aquatic invertebrates were less than 0.01. While reproduction effects were observed in chronic water-column invertebrate studies, chronic RQs range up to 0.22 for freshwater invertebrates and up to 0.19 for estuarine/marine invertebrates and are below the chronic LOC. There were no effects to sediment dwelling invertebrates.
- There are were no toxicological effects observed to aquatic vascular plants, and while effects on growth were observed for non-vascular plants it was at levels much higher (>100X) than EECs. All RQs were less than 0.01 for aquatic plants.

For terrestrial organisms, the risk assessment concluded:

- There were no risk concerns for non-target, non-listed birds (surrogates for reptiles and terrestrial-phase amphibians), mammals, honey bees, or terrestrial plants. LOC for non-listed birds and mammals is 0.5 for acute and 1 for chronic exposures. LOC for non-listed terrestrial plants is 1. Acute LOCs for honey bees is 0.4 and chronic LOC is 1. There were also no RQs above the LOC for listed birds (and reptiles and terrestrial-phase amphibians, for which birds are considered surrogates), mammals, or terrestrial invertebrates. The LOC for listed birds and mammals is 0.1 for acute and 1 for chronic exposures.
- Ipflufenoquin is practically non-toxic to mammals and bobwhite quail on an acute oral basis and to birds on an acute dietary basis. There was regurgitation in the passerine and mallard duck acute oral studies, but no mortality was observed. Acute oral and dietary toxicity to birds and the acute oral toxicity to mammals exposed to ipflufenoquin were non-definitive with calculated LD/LC_{50} values being greater than highest concentrations tested. Because non-definitive LD/LC_{50} values are not used to estimate risk, acute RQs were not calculated for birds or mammals. Instead, EPA compared the highest EEC to the most sensitive endpoint (i.e., regurgitation in the avian acute oral) in which the maximum

EECs were at least 6X lower than the most sensitive endpoint (i.e., regurgitation). Additionally, the EECs are at least 47X lower than the lowest dose that reported no mortality. Therefore, acute risk is anticipated to be low.

- While chronic studies in birds resulted in effects to growth and reproduction, there were no chronic LOC exceedances for birds (surrogates for reptiles and terrestrial-phase amphibians) of all sizes and across all types of diet assessed. Chronic RQs for birds range from 0.01 to 0.29. Additionally, while chronic studies for mammals resulted in decreased pup rate, chronic RQs ranged from <0.01 to 0.21 which do not exceed the LOC.
- On an acute basis, ipflufenoquin is practically non-toxic to honey bees. Acute RQs were not calculated for adult honey bees because the acute toxicity values were non-definitive (LD_{50} greater than highest concentration tested). However, EECs are at least two orders of magnitude below test concentrations. Acute larval RQs were 0.01. Therefore, EPA anticipates acute risk to honey bees from direct exposure to ipflufenoquin to be low. There were no chronic effects to adult bees. Chronic effects to larval bees resulted in decreased emergence. Chronic adult honey bee RQs ranged from 0.12 to 0.19, and chronic larval RQs ranged from 0.16 to 0.26 all of which are below the LOC. The honey bee risk assessment also serves as a conservative evaluation of risk to other non-listed species of bees that may forage on exposed pollen and nectar.[3]
- Honey bee toxicity data was also used as a surrogate for potential toxicity to other terrestrial arthropods, including listed invertebrate species. When considering conservative estimates of residues in arthropods and on potential dietary items (i.e. short grass) compared to concentration-based endpoints, EPA concluded that there was no risk to listed terrestrial invertebrates since estimated upper bound exposures were 1X to 2X below acute toxicity endpoints and 3X below chronic toxicity endpoints.
- Terrestrial plant toxicity studies (tested with only one concentration of 0.09 lbs a.i./A) resulted in EC_{25}s of >0.09 lbs a.i./A in both the seedling emergence and vegetative vigor studies (non-definitive endpoints as effects ≤25% in both studies). However, for some plant species (i.e., wheat, soybean, and onion) there were effects (11-13%) on growth, and so a definitive NOAEC was not established. RQs were not calculated for terrestrial plants. Since a definitive NOAEC has not been established, EPA has not made effects determinations for listed terrestrial plants or those listed species that have an obligate relationship with a terrestrial plant species. For non-listed species which uses the EC_{25} value, the test concentration rate (0.09 lbs a.i./A) is higher than the proposed maximum single application rate (0.065 lbs a.i./A). Therefore, the risk to non-listed terrestrial plants from the use of ipflufenoquin is considered low.

C. Comparable Chemistries

Ipflufenoquin is a quinoline fungicide which Nippon Soda Co. Ltd claims has an undetermined mode of action. Nippon Soda Co., Ltd., submitted a petition for reduced risk status for ipflufenoquin on pome fruits and almond, claiming that ipflufenoquin controls a broad spectrum of fungal diseases for the proposed uses. The Agency has identified cyprodinil, difenoconazole, fluopyram, myclobutanil, pyraclostrobin, trifloxystrobin as comparable fungicides for the pome

[3] USEPA. 2014. Guidance for Assessing Pesticide Risks to Bees. Environmental Fate and Effects Division, Office of Pesticide Programs, U.S. Environmental Protection Agency. June 23, 2014.

fruit (Crop Group 11-10) use, as well as azoxystrobin, boscalid, cyprodinil, fluopyram, propiconazole, pyraclostrobin, trifloxystrobin as comparable fungicide for use on almonds. Overall, ipflufenoquin is generally less toxic or of similar toxicity to the comparable fungicides with few exceptions for chronic toxicity to freshwater fish and estuarine/marine invertebrates. However, as noted above, there are no risk concerns for freshwater fish or estuarine/marine invertebrates. This comparison reflects a snapshot of the most sensitive, Agency-reviewed toxicity studies and does not represent a full quantitative comparative risk analysis, which would involve integrating additional information such as the magnitude and duration of potential environmental exposures.

For acute oral and dietary toxicity to avian species, ipflufenoquin resulted in non-definitive values, which is similar to many of the comparable fungicides. Ipflufenoquin is less toxic than myclobutanil and difenoconazole and of equal toxicity to the remaining compounds. For chronic toxicity to avian species, ipflufenoquin is similar in toxicity to the comparable fungicides.

For acute dietary toxicity to mammalian species, ipflufenoquin is less toxic than myclobutanil, propiconazole and difenoconazole but of similar toxicity to the remaining compounds. For chronic toxicity to mammalian species, ipflufenoquin is less toxic than propiconazole, azoxystrobin, fluopyram and trifloxystrobin and similar in toxicity to the other comparable fungicides.

For acute oral and contact exposure to honey bees, ipflufenoquin resulted in non-definitive toxicity values which was similar to the alternatives where data were available. For adult chronic exposures, ipflufenoquin was less toxic compared to myclobutanil and pyraclostrobin and similar in toxicity to boscalid and difenoconazole. For acute larval exposure, ipflufenoquin was less toxic than difenoconazole and pyraclostrobin and similar in toxicity to propiconazole with no data available for the other compounds. For chronic larval exposure, ipflufenoquin was similar in toxicity to the comparable fungicides where data were available.

For acute toxicity to freshwater and estuarine/marine fish, ipflufenoquin is of lower toxicity compared to pyraclostrobin and trifloxystrobin and similar for the rest of the chemicals. For chronic toxicity to freshwater and estuarine/marine fish, ipflufenoquin is of lower toxicity compared to difenoconazole, pyraclostrobin and trifloxystrobin and is similar in toxicity to the remaining compounds, except for freshwater fish which exhibits greater toxicity when compared to myclobutanil.

For acute toxicity to freshwater invertebrates, ipflufenoquin is less toxic than pyraclostrobin, boscalid, cyprodinil and trifloxystrobin and similar in toxicity to the remaining comparable compounds. For acute toxicity to estuarine/marine invertebrates, ipflufenoquin is of similar toxicity to propiconazole, myclobutanil, boscalid, and fluopyram but is less toxic to the remaining comparable compounds. For chronic toxicity to freshwater aquatic invertebrates, ipflufenoquin is more toxic compared to myclobutanil, and of lower or similar toxicity to the other alternatives. For chronic toxicity to estuarine/marine aquatic invertebrates, ipflufenoquin is more toxic than boscalid and propiconazole but less or similarly toxic than the remaining compounds.

For acute toxicity data for aquatic plants, ipflufenoquin was generally less toxic than most of the alternative compounds. For terrestrial plants, ipflufenoquin was generally of similar toxicity to the comparable fungicides, as many of them also had non-definitive endpoints.

D. Benefits Assessment

As part of the registration process, EPA assesses the benefits of the new pesticide as compared to available conventional fungal control methods based on information submitted by the registrant and publicly available scientific literature.

The registrant claims that the registration of ipflufenoquin will provide the following benefits:

- Comparable or superior control of economically important and difficult-to-control fungal pests and crop safety comparable to alternative fungicides;
- Attributes which facilitate Resistance Management (RM) and Integrated Pest Management (IPM) programs;
- A novel mode of action (MOA) with no known cross-resistance to help prevent resistance development.

EPA expects ipflufenoquin to provide growers with a fungicidal tool to control economically important fungal pests in proposed use sites and manage fungicide resistance. If confirmed by further research, a novel MOA would be useful for resistance management in the proposed use sites.

Ipflufenoquin is proposed to be labeled for control of scab and powdery mildew on pome fruits (crop group 11-10) and brown rot blossom blight, shot hole, anthracnose, scab, and Alternaria leaf spot on almond. These are all important diseases in their respective crop systems which need to be controlled and commonly require management with pesticides to prevent yield or quality losses. The Pacific Northwest Plant Disease Handbook calls apple scab "common and destructive" and indicates that fungicides are necessary for its management.[4] Additionally, almond diseases which ipflufenoquin is proposed to be labeled to control all have potential to be severe unless managed with fungicides.[5] Fungicide resistance has also been detected in some of these diseases, such as in apple scab and in Alternaria leaf spot, indicating a need for efficacious fungicides with new modes of action in order to maintain effective control of these diseases.[1,6]

The registrant submitted comparative efficacy data of ipflufenoquin and currently used fungicides to support benefits claims for all diseases. The proposed labeled application rate of ipflufenoquin controlled disease comparably to the labeled application rate of industry standard

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[4] Pscheidt, J.W., and Ocamb, C.M. (Senior Eds.). Apple (Malus spp.) Scab. 2021. In: 2021 Pacific Northwest Plant Disease Management Handbook. Oregon State University.

[5] Haviland DR, Symmes EJ, Adaskaveg JE, Duncan RA, Roncoroni JA, Gubler WD, Hanson B, Hembree KJ, Holtz BA, Stapleton JJ, Tollerup KE, Trouillas FP, Zalom FG. Revised continuously. UC IPM Pest Management Guidelines: Almond. UC ANR Publication 3431. Oakland, CA.

[6] Luo, Y., Ma, Z., Reyes, H.C., Morgan, D.P., Michailides, T.J. 2007. Using real-time PCR to survey frequency of azoxystrobin-resistant allele G143A in Alternaria populations from almond and pistachio orchards in California. Pesticide Biochemistry and Physiology.

fungicides.[7] EPA expects ipflufenoquin to be a helpful tool in chemical management of its labeled diseases.

Additionally, the registrant claims that the mode of action of ipflufenoquin is novel. If confirmed, a novel mode of action will be helpful for fungicide resistance management; however, EPA is not able to verify this claim. Sensitivity tests conducted on fungicide-resistant isolates of *Venturia* sp. and *Botrytis* sp., common diseases of apple for which growers spray, has demonstrated that there is no cross-resistance with FRAC groups 1, 2, 9, 10, 11 and 29, and current research results indicate that ipflufenoquin's MOA differs from the FRAC group 7 and 11 fungicides studied.[8] This is especially important for its target diseases that have already developed resistance to other fungicides, such as apple scab and Alternaria leaf spot in almond.[1,3] Ipflufenoquin can be used as part of an integrated disease control program alongside cultural and biological controls and with fungicides of other modes of action as part of a resistance management strategy for the approved crops.

E. Greater than Additive Effects

Recently, some chemical companies have made claims in patents that certain combined mixtures of pesticides elicit synergistic effects, meaning that when the chemicals are mixed the combined effect is greater than the sum of the individual effects of each chemical.

The EPA has developed an interim process to evaluate effects of mixtures of active ingredients based on patents granted by the U.S. Patent and Trademark Office (PTO) on the basis of the applicant showing the combined effects of the mixture are synergistic (i.e., the effect of a mixture of pesticides is greater than the sum of the individual effects). To ensure that effects data on the mixture that may be relevant to ecological risk assessments are considered, the EPA requested that registrants of new chemicals submit toxicity data for mixtures that were provided to the U.S. PTO. The EPA provided guidance to assist registrants in identifying relevant data for submission. Nippon Soda Co., Ltd. completed a search of U.S. patent data to identify any claims of synergy (or greater than additive effects) with other currently registered pesticides according to the guidance and submitted corresponding data to the EPA for ipflufenoquin.

In their submission, Nippon Soda Co., Ltd. identified 39 patents containing key words specific to ipflufenoquin and greater than additive (GTA) effects, with a refined subset of 20 pertaining to pesticide products. Of those, the registrant stated that only 7 patents explicitly mentioned the compound of interest. Within these 7 patents, the company stated that no testing of mixtures containing ipflufenoquin (NF-180) was reported. Therefore, none of these patents are relevant to a GTA evaluation and, therefore, do not meet the EPA criteria for consideration in the ecological risk assessment process.

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[7] Nelson, JE, Schneider, LL, Wrubel, JJ, Knox, K, Barney, SM. 2019. A Benefits Document Supporting the Registration of Ipflufenoquin (NF-180) to Control Economically Important Diseases in Pome Fruit and Almonds. Nippon Soda Company. MRID: 50921058

[8] Nelson, JE, Schneider, LL, Wrubel, JJ, Knox, K, Barney, SM. 2019. A Benefits Document Supporting the Registration of Ipflufenoquin (NF-180) to Control Economically Important Diseases in Pome Fruit and Almonds. Nippon Soda Company. MRID: 50921058Id.

Therefore, based on the information provided by Nippon Soda Co., Ltd., the Agency concludes that the identified patent data containing information on ipflufenoquin contained no GTA effects information relevant to the ipflufenoquin ecological risk assessment.

V. PUBLIC COMMENTS

On May 27, 2020, the EPA published a Notice of Receipt (NOR) in the Federal Register notifying that EPA was in receipt of an application to register pesticide products containing an active ingredient not included in any currently registered pesticide products (ipflufenoquin) and announced a public comment period of 30 days. Three comments were received on the NOR and can be found in docket ID number EPA-HQ-OPP-2020-0225 at regulations.gov. These comments will be addressed in the Agency's Final Decision document in order to respond to all comments on this action comprehensively, including comments received during the 15-day public comment period on this proposed decision. The EPA also published a Notice of Filing (NOF) on May 29, 2020 for a 30-day comment period. No comments were received on the NOF.

VI. PROPOSED REGULATORY DECISION

In accordance with FIFRA, the EPA registers a pesticide when it determines that it will not cause unreasonable adverse effects on humans or the environment, while taking into account the economic, social, and environmental costs and benefits of the use of the pesticide. When a registration involves food uses, this determination also includes a finding that dietary risk from pesticide residues in food meet the safety standard of section 408 of the Federal Food, Drug and Cosmetic Act (FFDCA) ("a reasonable certainty of no harm…"). Under FIFRA, the EPA is charged with balancing risks posed by the use of a pesticide against its benefits. The EPA must determine if the benefits in light of its use outweigh the risks in order for the EPA to register a pesticide. FIFRA section 3(c)(5) specifically requires approving of a registration if EPA determines:

i. its composition is such as to warrant the proposed claims for it;

ii. its labeling and other material required to be submitted comply with the requirements of this Act;

iii. it will perform its intended function without unreasonable adverse effects on the environment; and

iv. when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment.

A. Rationale and Risk Mitigation

The EPA is proposing to issue registrations for the following products as part of the registration of the active ingredient, ipflufenoquin:

Name	File Symbol	Active Ingredient(s)
Kinoprol Technical	8033-RUN	99.2% ipflufenoquin
Kinoprol 20 SC	8033-RGO	18.4% ipflufenoquin

EPA reviewed the compositions of both products and determined that the claims made are warranted and the information supports the approval of the registrations. The labeling from the registrants contains all the necessary requirements and restrictions and complies with the requirements of FIFRA. EPA received studies and other information, necessary to comply with the data requirements for the uses of these products. The Agency also reviewed a large body of data and information to determine how these products could be used to determine the risks and benefits. All of these evaluations informed EPA's determination that registering these products will not generally cause unreasonable adverse effects on the environment when used in accordance with widespread and commonly recognized practice.

In making a determination as to unreasonable adverse effects, EPA is charged with considering the economic, social, and environmental costs and benefits of the use of the pesticide. EPA must determine if the benefits outweigh any potential risks of concern as well as adverse impacts in order for the Agency to determine the product will not generally cause unreasonable adverse effects.

The database is considered complete for assessment of risks to human health and the environment, and there are no data gaps.

A conservative risk assessment did not identify any LOC exceedances for human health when ipflufenoquin is used according to label directions and classified ipflufenoquin as "Not Likely to be Carcinogenic to Humans" when used according to label directions. Tolerances for residues of ipflufenoquin in or on crop commodities on which this chemical is used will be published by the time any registrations are issued for ipflufenoquin.

There were no LOC exceedances for non-listed species including all aquatic species, birds, mammals, and terrestrial plants. The EPA has made NE Determinations for all listed taxa except for listed terrestrial plants, or those species that have an obligate relationship with a terrestrial plant species. EPA has also made NE determinations for the designated critical habitats of all listed species, except for those listed species with defined Principle Constituent Elements (PCEs) or Physical or Biological Features (PBFs) that indicate obligate relationships to a specific terrestrial plant species, because the proposed uses of ipflufenoquin will not adversely modify those critical habitats.

The registrant submitted comparative efficacy data of ipflufenoquin and currently used fungicides to support benefits claims for diseases mentioned above. Ipflufenoquin can be used as part of an integrated disease control program alongside cultural and biological controls and with fungicides of other modes of action as part of a resistance management strategy for the approved crops.

The EPA is not requiring any additional data to assess risk to human health or the environment in order to make our registration determination.

No risks of concern were identified for human health or the environment. The Agency has concluded that the benefits of the proposed registration outweigh the potential risks. Considering the assessed risk to human health and the environment and the identified benefits, the Agency concludes that ipflufenoquin meets the regulatory standard under FIFRA. Therefore, the EPA concludes that the use of ipflufenoquin as a foliar fungicide on pome fruit crop group 11-10 and almonds will not cause unreasonable adverse effects on the environment and meets the criteria for unconditional registration under FIFRA section 3(c)(5).

B. Label Requirements

The following label language is required for protection of workers:

An REI of 4 hours is adequate to protect agricultural workers from post-application exposures to ipflufenoquin.

Personal Protective Equipment:

Mixers, loaders, applicators and other handlers must wear:

- Long-sleeved shirt and long pants
- Socks and shoes
- Chemical resistant gloves made of barrier laminate or butyl rubber ≥ 14 mils or nitrile rubber ≥ 14 mils or neoprene rubber ≥ 14 mils or polyvinyl chloride (PVC) ≥ 14 mils or Viton ≥ 14 mils.

VII. SUPPORTING DOCUMENTS

All supporting documents listed below can be found in docket ID number EPA-HQ-OPP-2020-0225 at regulations.gov.

- Ipflufenoquin. Human Health Risk Assessment for Proposed Section 3 Registration of the New Active Ingredient for Uses on Pome Fruit (Crop Group 11-10) and Almond. (DP #455017)
- Ipflufenoquin: Ecological Risk Assessment for Section 3 New Chemical Registration. (DP #455013)
- Ipflufenoquin: Drinking Water Exposure Assessment Supporting New Chemical Registration. (DP #459589)
- Ipflufenoquin. Occupation and Residential Exposure Assessment for the Proposed Uses of the New Active Ingredient Ipflufenoquin. (DP #459445)
- Ipflufenoquin. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section 3 Registration Action the New Active Ingredient for Uses on Fruit, Pome (Crop Group 11-10) and Almonds. (DP #459729)
- Review of Submitted Data Relating to Claims of Greater-than-Additive (GTA) Mixture Toxicity Associated with the Proposed New Active Ingredient, Ipflufenoquin (PC code 129120). (DP #459531)

- Ipflufenoquin: Comparison of Hazard Profile for Comparable Fungicides. (DP #460536)
- Draft Label: Kinoprol Technical (8033-RUN)
- Draft Label: Kinoprol 20 SC (8033-RGO)